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Non-coeliac gluten sensitivity: piecing the puzzle together

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Abstract

The avoidance of wheat- and gluten-containing products is a worldwide phenomenon. While coeliac disease is well-established, much remains unknown about whether gluten can be a trigger of gastrointestinal and/or extra-intestinal symptoms in patients without coeliac disease. In this article, we discuss the latest scientific evidence and our current understanding for the possible mechanisms of this largely ambiguous group, termed 'non-coeliac gluten sensitive' (NCGS). We can conclude that NCGS should be regarded as an independent disease outside of coeliac disease and wheat allergy, and that the number of patients affected is likely to be limited. Many questions remain unanswered and it needs to be verified whether the elimination of dietary gluten alone is sufficient for the control of symptoms, and to understand the overlap with other components of wheat.

Keywords

gluten, non-coeliac gluten sensitivity, gluten-free, FODMAPs, gastrointestinal diseases, coeliac disease, wheat allergy

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Background

Our understanding of the increasing worldwide demand for gluten- and wheat-free products has not been supported by good scientific evidence. Aside from the well-defined medical condition of coeliac disease, gluten is blamed as a trigger of symptoms by 20-45% of adults who self-report food hypersensitivity.[1] The role of dietary components in inducing gastrointestinal (GI) symptoms is a complex area and the understanding of dietary triggers of GI symptoms is not complete. The thin line between coeliac disease, wheat allergy, irritable bowel syndrome and non-coeliac gluten sensitivity (NCGS) is not always clearly distinguishable; making it difficult to exactly differentiate between these disorders (outlined in Table 1). Unlike coeliac disease and wheat allergy, NCGS is an unclear and controversial entity.

Terminology

Coeliac disease occurs when genetically susceptible patients are exposed to dietary gluten, the major protein in wheat, rye, barley and related grains, activating a specific immune response. Coeliac disease affects at least 1% of Western populations and leads to small bowel damage and elevated coeliac-specific antibodies.[2] More than 95% of patients with coeliac disease carry the HLA-DQ2 or HLA-DQ8 heterodimers and the rest express HLA-DQ that contain half of the coeliac associated molecules.[2] The only known treatment is a lifelong, strict gluten-free diet (GFD). After digestion, gluten peptides are deaminated by the tissue-transglutaminase and presented to activated T cells, which then produce interferon-γ and other cytokines, leading to mucosal damage of the small bowel. Many of the classical clinical symptoms seen in coeliac disease picture malabsorption (diarrhoea, abdominal pain, bloating, wind, distension). In addition, non-specific signs and symptoms (iron deficiency anaemia, osteoporosis, fatigue) or even asymptomatic presentation are now accepted to be common.[3]

Wheat allergy is an IgE mediated reaction to the insoluble gliadins of wheat. The symptoms of wheat

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Table 1. Summary of gluten-related disorders

Gluten-related disorders	Key symptoms	Diagnosis
Coeliac disease	Malabsorption: diarrhoea, abdominal pain, bloating	HLA genotyping: HLA-DQ2 or HLA-DQ8 positive
	Iron deficiency anemia, fatigue	Measuring antibodies to check for elevated antibodies to gliadin
	Osteoporosis	Biopsy of the intestine (gold standard)
Wheat allergy	Itching and swelling in the nose and throat, rash, wheezing	IgE measurements
	Anaphylaxis	
IBS	Bloating, abdominal pain, diarrhoea, wind, altered bowel habits	Functional symptoms that cannot be explained by any other physiological, biochemical or inflammatory cause (standardised by Rome criteria)
NCGS	IBS-like symptoms	Different steps needed:
	Fatigue, headache, fibromyalgia-like joint or muscle pain	1. Definitive exclusion of coeliac disease
	Leg or arm numbness, foggy mind, skin rash, anemia	2. Exclusion of other dietary triggers (FODMAPs)
	Depression, anxiety	3. Dietary gluten exclusion and rechallenge

allergy develop within minutes to hours after gluten ingestion and include itching and swelling in the mouth, nose, eyes and throat, skin rash and wheezing, and life-threatening anaphylaxis. The GI manifestations of wheat allergy may be similar to those of coeliac disease but instead does not cause permanent GI damage.[4]

Irritable bowel syndrome (IBS) is a disorder characterised by GI symptoms (abdominal pain, diarrhea), with no abnormal pathology and affects 15% of the population.[5] IBS presents a major challenge for clinicians, because of multiple contributing factors and conflicting evidence for management strategies and suitable pharmaceutical therapies.

Non-coeliac gluten sensitivity (NCGS) is a condition where intestinal and extra-intestinal symptoms are triggered by gluten ingestion in the absence of coeliac disease and wheat allergy, as defined by discussions held at three different international consensus conferences.[6–8] The clinical picture of NCGS is a combination of IBS-like symptoms, behaviour disturbances and systemic manifestations.[8] Attempts to characterise NCGS have shown that these systemic manifestations (tiredness, headache, fibromyalgia-like joint or muscle pain, leg or arm numbness, 'foggy mind,' dermatitis or skin rash, depression, anxiety, and anaemia) may be common.[9,10]

The symptoms occur soon after gluten ingestion, improving or disappearing within hours or a few days after gluten withdrawal and then relapsing following its reintroduction.[7] Despite the first reports on NCGS dating from 1978,[11–13] much remains unknown about the condition. Recently, publications including a few well-conducted double-blinded randomized placebo-controlled trials have provided some evidence, opening the door to discussions on how to best distinguish NCGS from coeliac disease, wheat allergy and IBS. Below we present the most up-to-date understanding of the nature of NCGS including its trigger, diagnosis, risks and treatment.

Distinguishing wheat and gluten

The evidence base for non-gluten components of wheat (fructans) inducing symptoms in many patients with IBS is convincing.[14–16] Short-chain fructans (fructo-oligosaccharides) are the main carbohydrate component of wheat and are poorly absorbed in the small intestine. This poor absorption increases delivery of water and fermentable substrates to the colon, which can result in increased gas production and GI symptoms in patients with IBS. Similarly behaved carbohydrates have been grouped together and termed FODMAPs: Fermentable Oligo-, Di-, and Mono-saccharides And Polyols. A diet low in FODMAPs is an evidence-based strategy leading to symptomatic improvement in 74% of patients with IBS.[17] FODMAPs are found in a wide variety of foods, including lactose (in milk), excess fructose (in pears, apples), fructans and fructo-oligosaccharides (in artichoke, garlic, onions, wheat and rye), galacto-oligosaccharides (GOS; stachyose and raffinose in legumes), and sugar polyols (sorbitol and mannitol in stone fruits and artificial sweeteners).[18–21] Wheat- and rye-derived products often

contain the highest FODMAP content, predominantly fructans and GOS. Cereal products with the lowest FODMAP contents are mostly gluten-free, based on rice, oat, quinoa and corn ingredients.

Other grain proteins, termed α-amylase/trypsin inhibitors (ATIs), have also been suggested to evoke symptoms in NCGS. ATIs are low molecular weight proteins found in wheat and related cereals that may induce innate immune responses activating the TLR4 complex.[22] Some recent in vitro and in vivo work has suggested that these ATIs may increase the gluten-specific T-cell response in coeliac disease.[22] Another component in wheat, wheat lectin agglutinin (WGA), has also shown increased intestinal permeability and potential activation of the immune system.[23] This early evidence is in need of further clinical studies to establish the role in humans.

There is not yet any direct evidence to suggest that a GFD is detrimental to follow outside of coeliac disease, however there is data that shows signs of nutritional deficiency in treated coeliac patients.[24] Unnecessarily following restrictive diets raise two main concerns. Firstly, the prescription of a GFD for GI and other symptoms may lead to the under diagnosis of coeliac disease. Two in three patients with self-perceived NCGS do not have coeliac disease adequately excluded,[25] which increases patients' risk of inadequate management and screening of associated complications if left untreated (reduced bone health, long-term mortality). Secondly, the GFD can be markedly restrictive, presents challenges when eating at places other than home and can be nutritionally inadequate, especially in fibre and B-vitamins.[26] In addition, at least 45% of patients with self-perceived NCGS self-initiate the GFD and have not undergone dietetic education to ensure nutritional adequacy.[10] Long-term restrictive diets, particularly avoidance of wheat-based products, are likely to have health implications especially given their important role in bowel health.

The current evidence for NCGS

Studies in vitro and animal experiments provide clues to possible mechanisms that can be applied to subsequent human studies, for example gluten-induced effects on epithelial permeability, apoptosis or oxidative stress. Nevertheless, translation into human studies has shown varying pathology, immunology and conflicting mucosal immunological events.[27–30] Interpreting and drawing definitive conclusions from the few clinical trials that focus on NCGS is difficult because of weaknesses in the study design or execution, for example inconsistent definition of NCGS and inclusion criteria, small number of participants, inclusion of participants with elevated markers of coeliac disease (intraepithelial lymphocytosis in the duodenum and evidence of immunological activation), or the non-distinction between gluten and other wheat components.

Currently, there is some evidence in patients believed to have NCGS of gluten-induced activation of innate immunity in the absence of detectable changes in intestinal barrier function.[31] Furthermore, in an Italian study, positive coeliac serology (IgG AGA) was shown in more than half of cases but mostly without specific antibodies associated with coeliac disease (IgG deamidated gliadin peptide antibodies, IgA tissue transglutaminase antibodies or IgA endomysial antibodies).[32] Genetic predisposition to coeliac disease has also been suggested as a factor for NCGS where patients carrying the HLA-DQ2 allele, but without villous atrophy on duodenal biopsy, have been shown to symptomatically improve on a GFD.[27,28]

The best, well-controlled, double-blind, placebo-controlled randomised studies have only recently been published.[33–35] Vasquez-Roque et al. reported that in patients with diarrhoea-predominant IBS, consumption of a gluten-containing diet was associated with higher small bowel permeability than with a GFD.[35] This effect cannot be concluded to be gluten-specific, but rather is attributable to the GFD. In 2011, Biesiekierski et al showed that 16 grams of gluten per day induced a rapid onset of GI symptoms and tiredness within the first week of a 6-week intervention.[33] A follow-up dietary trial, conducted by the same research group, and designed to be of tighter control (using a randomised, double-blind, placebo-controlled, dose-finding, crossover design) showed significant improvement in GI symptoms and tiredness levels during a low FODMAP-run-in period, but showed no effect of gluten in inducing change in any symptom in either a 7-day gluten challenge or 3-day rechallenge.[34] These results highlight the likely impact that reducing FODMAPs and other dietary triggers may have in this population. Furthermore, these inconsistent results show the importance of having specific inclusion and recruitment criteria.

Potential mechanisms

Gastrointestinal symptoms – In two highly selected, tightly-controlled human dietary trials, the gluten response could not be reproduced.[33,34] Although all of the participants originally believed themselves to have NCGS, their symptom response showed no gluten-specificity and appeared to be a random event. There were no differences found in any biomarker assessed to indicate a potential mechanism. In contrast, the likely role FODMAPs have in inducing GI symptoms in NCGS patients is plausible – many self-perceived NCGS patients still had significant symptoms despite

a GFD and there was significant improvement of GI symptoms by following a low FODMAP diet for two weeks.[34] The physiological effects of FODMAPs are well-understood, including osmotic activity[36] and rapid fermentation[37] by virtue of their poor absorption in the small intestine, both inducing luminal distension and consequently GI symptoms.[15,36,37]

Extra-intestinal symptoms – Non-IBS symptoms and other extra-intestinal symptoms are often reported by people who believe they have NCGS,[10] and in addition, complaints of headache/migraine, musculoskeletal pain, heartburn, mood change, itchiness/rash and forgetfulness have been recorded.[38] Therefore, it remains to be proven if and how gluten has direct causal effects on extra-intestinal symptoms in patients without coeliac disease.

Mental health – In patients with functional GI disorders, anxiety and depression are present, particularly as a personality trait[39], and may play a role in the genesis and/or the perception of symptoms. Short-term exposure to gluten specifically induced current feelings of depression in patients with self-reported NCGS, with no effect on other indices or on emotional disposition.[40] These demonstrated depressive symptoms may lead to participants being more concerned about their symptoms and more sensitive in relation to visceral sensation. Such findings might explain the basis for patients reportedly ''feeling better'' on a GFD despite continuation of GI symptoms. It may also give some insight behind why the effect of gluten on GI (and possibly extra-intestinal) symptoms appears to be random, given there are so many influential variables inducing psychological dysfunction (i.e., biological and psychosocial factors).[41] Other possibilities for how gluten may be related to depression include abnormalities of serotonin production,[42] or gluten exorphins interfering with the CNS,[43] or changes in the gut microbiota.[44] It should be emphasized that the tool used to assess depression in this study was one self-administered questionnaire, and the clinical significance of these findings requires further research using additional measures of depression and of longer duration. Currently, there is no evidence for efficacy of gluten exclusion in mental disorders,[8,45] therefore care must be given when discussing these early results and awareness given to understanding that a major effect of gluten in NCGS patients may be in the perception of their general well-being.

Translating research and clinical implications

Without convincing, reproducible results from clinical trials showing effects on inflammatory or immune markers, NCGS should be regarded as a sub-group of IBS and distinct from coeliac disease. Lowering the dietary intake of FODMAPs continues to be the first line therapy for patients experiencing GI symptoms. The use of dietary gluten restriction in the management of gut symptoms should be done under dietetic supervision after exclusion of coeliac disease. The existence of NCGS remains unsubstantiated and more definitive research is needed to fulfil our understanding.

Many questions remain unanswered, including how common NCGS is, how it can be reliably identified and what its underlying mechanisms are. Self-reporting can be inaccurate and there is likely to be a major difference in perceived versus actual NCGS.[10] Indeed, these survey findings confirmed prior investigations,[46,47] finding large discrepancies between perceived and proven food hypersensitivity. Ideally, identification of biomarker(s) would allow the development of an objective diagnostic test. Much research is still needed to fulfil our understanding of NCGS, importantly the clinical phenotype to allow the accurate prevalence to be defined and understanding whether a broader NCGS group outside of IBS specifically exists. The blinded, placebo-controlled, rechallenge study design is not a methodology that works well with population studies, but is currently best practice. Large population study designs, similar to early prevalence studies of coeliac disease may need to be undertaken.

Determining the mechanism is difficult when there is no current way of specifically defining the condition. A range of different markers assessing immune reactions (predominantly coeliac-related and adaptive immune pathways), inflammatory responses and poor digestibility of the gluten protein have been investigated. Future studies must not rule out analysing similar mechanistic concepts, especially at the tissue level. It is of paramount importance that this analysis should be undertaken in patients who express positive symptom responses to gluten. If innate immune responses were to be responsible for NCGS, it requires explanation how it induces systemic symptoms. One speculative hypothesis is that gluten may not be directly involved in the triggering of GI symptoms, but rather in the pathogenesis of visceral hypersensitivity. There may be two different effects occurring: first, gluten is sensitising the visceral (enteric) nervous system especially the mechanoreceptors and, secondly, the poorly absorbed, rapidly fermentable FODMAPs are then mainly responsible for inducing GI symptoms.

Other questions remain unanswered, including whether the gluten-mediated effect is an all-or-none or a dose-related phenomenon and what part of the gluten is responsible. Furthermore, randomised trials on NCGS in children are lacking. High quality, well-controlled research in human trials is difficult to carry out and is fraught with its own hurdles. Important considerations for future well-designed dietary trials

investigating NCGS include high order effects in cross-over designs, large nocebo effects, patient selection and clear entry criteria, methods of gluten challenge, properties of what is used as the placebo use, ensure successful blinding, well-defined endpoints, control of confounding dietary factors and trying to ensure that the protocol and provision of food is well received by participants.[48]

Conclusions

There is some evidence that NCGS may exist, but probably only in a small number of people. The self-reported NCGS patients are heterogeneous (in their range of reported symptoms, clinical histories and characteristics) and are highly suggestible, making a largely difficult patient group to study. Much of the confusion and controversy has arisen in part from a failure to distinguish clearly between the gluten and fructan components of wheat. Indeed, patients who believe they have NCGS are likely to benefit from lowering their dietary intake of FODMAPs. Providing the careful design of clinical trials, the next several years will provide a stronger quality of evidence and exciting key pieces to understand this NCGS puzzle.

Conflict of interest

There were no conflicts of interest to declare.

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